

CLAIMS

1. A method of modifying drug pharmacokinetics which comprises altering the activity of SXR on expression levels of *CYP2C8* or *MDR1*.
2. A method of claim 1 wherein said alteration in SXR activity alters *CYP2C8* expression.
3. A method of claim 1 wherein said alteration in SXR activity alters *MDR1* expression.
4. A method of modifying multiple drug resistance which comprises altering SXR activity.
5. A method of claim 1 or 4 wherein drug catabolism is altered.
6. A method of claim 5 wherein drug catabolism is reduced.
7. A method of claim 5 wherein drug catabolism is increased.
8. A method of claim 1 or 4 wherein drug intestinal efflux is altered.
9. A method of claim 8 wherein drug intestinal efflux is reduced.
10. A method of claim 8 wherein drug intestinal efflux is increased.

11. A method of claim 1 or 4 wherein drug oral absorption is altered.

12. A method of claim 11 wherein drug oral absorption is reduced.

13. A method of claim 11 wherein drug oral absorption is increased.

14. A method of claim 1 or 4 wherein drug biliary excretion is altered.

15. A method of claim 14 wherein drug biliary excretion is reduced.

16. A method of claim 14 wherein drug biliary excretion is increased.

17. A method of claim 1 or 4 which comprises altering SXR mRNA levels.

18. A method of claim 1 or 4 which comprises altering SXR protein levels.

19. A method of claim 1 or 4 which comprises altering the ability of SXR to recruit coactivator.

20. A method of claim 1 or 4 which comprises altering the displacement of corepressor from SXR.

21. A method of claim 1 or 4 wherein said drug is a taxane.

22. A method of claim 1 or 4 which comprises administering an SXR antagonist.

23. A method of claim 22 wherein said SXR antagonist is ecteinascidin-743.

24. A method of claim 1 or 4 which comprises administering an SXR agonist.

25. A method of claim 1 or 4 which comprises administering a ribozyme which cleaves mRNA encoding SXR, an SXR coactivator or an SXR corepressor.

26. A method of claim 1 or 4 which comprises administering an antisense oligonucleotide which suppresses transcription or translation of SXR, an SXR coactivator or an SXR corepressor.

27. A method of identifying drugs with improved pharmacokinetic properties or activity which comprises screening drug candidates for their ability to modulate SXR.

28. A method of claim 27 which comprises identifying drugs having altered efflux characteristics by screening drug candidates for their ability to modulate the activity of SXR on expression levels of *CYP2C8* or *MDR1*.

29. A method of claim 27 which comprises identifying drugs having altered catabolism by screening drug candidates for their ability to modulate the activity of SXR on expression levels of *CYP2C8* or *MDR1*.

30. A method of claim 27 which comprises identifying drugs having altered oral bioavailability by screening drug candidates for their ability to modulate the activity of SXR on expression levels of *CYP2C8* or *MDR1*.

31. A method of claim 27 which comprises identifying drugs having altered biliary excretion by screening drug candidates for their ability to modulate the activity of SXR on expression levels of *CYP2C8* or *MDR1*.

32. A method of any of claims 27-31 wherein said drug candidates are taxanes.

33. A method of any of claims 27-32 which comprises monitoring SXR activity in cells *in vivo* or *in vitro*.

34. A method of claim 33 wherein said monitoring of SXR activity comprises monitoring the expression of an endogenous SXR regulated gene.

35. A method of claim 34 wherein said endogenous SXR regulated gene is a gene selected from the group consisting of *CYP3A4*, *CYP2C8* and *MDR1*.

36. A method of claim 33 wherein said monitoring of SXR activity comprises monitoring the expression of a synthetic reporter gene under the control of control elements responsive to SXR.

37. A method of claim 33 wherein said monitoring of SXR activity comprises monitoring the expression of a chimeric

gene, wherein the protein encoded by said chimeric gene maintains the ability to respond to SXR ligands.

38. A method of any of claims 27-31 which comprises monitoring SXR activity in cells *in vitro*.

39. A method of claim 38 wherein said monitoring of SXR activity comprises monitoring coactivator recruitment.

40. A method of claim 38 wherein said monitoring of SXR activity comprises monitoring corepressor displacement.

41. A method of claim 38 wherein said monitoring of SXR activity comprises monitoring SXR binding to DNA response elements in regulatory sequences that control expression of *CYP2C8*, *CYP3A4* or *MDR1* genes.

42. A method of claim 38 wherein said monitoring of SXR activity comprises monitoring SXR binding or SXR/RXR binding to nucleotide sequences that bind to SXR or to the SXR/RXR complex.

43. A method of claim 38 wherein said monitoring of SXR activity comprises monitoring SXR/RXR interaction.

44. A method of identifying drugs that do not modulate SXR activity which comprises screening drug candidates for their inability to:

- (a) modulate the activity of SXR on expression levels of *CYP2C8* or *MDR1*;
- (b) modulate the expression of *CYP3A4*;
- (c) modulate the expression of *CYP2C8*;

- (d) modulate the expression of *MDR1*;
- (e) modulate the expression of a synthetic reporter gene  
10 under the control of control elements responsive to SXR;
- (f) modulate the expression of a chimeric gene, wherein  
the protein encoded by said chimeric gene maintains the ability  
to respond to SXR ligands;
- (g) modulate SXR coactivator recruitment;
- 15 (h) modulate SXR corepressor displacement;
- (i) modulate SXR binding to DNA response elements in  
regulatory sequences that control expression of *CYP2C8*, *CYP3A4*  
or *MDR1* genes; or
- (j) modulate SXR/RXR interaction.

45. A drug identified by a method of any of claims 27-31,  
34-37 or 39-44.

46. A method of screening patients to predict  
responsiveness to a pharmacologic agent, which comprises:

- (a) obtaining a biological sample from said patient;
- (b) screening said biological sample for an SXR parameter  
5 selected from the group consisting of SXR mRNA levels, SXR  
protein levels, SXR coactivator levels, SXR-coactivator  
interactions, SXR corepressor levels, SXR-corepressor  
interactions, SXR polymorphisms, SXR mutations, expression of  
an endogenous SXR regulated gene, and levels of an endogenous  
10 SXR ligand.

47. A method of claim 46 wherein said biological sample is  
screened for expression of an endogenous SXR regulated gene.

48. A method of claim 47 wherein said endogenous SXR regulated gene is a gene selected from the group consisting of CYP3A4 and CYP2C8.

49. A method of claim 46 wherein said responsiveness to a pharmacologic agent is responsiveness to a therapeutic effect.

50. A method of claim 46 wherein said responsiveness to a pharmacologic agent is responsiveness to a toxic effect.

51. A method of claim 44 wherein said responsiveness to a pharmacologic agent is responsiveness to a drug interaction.

52. A method of claim 44 wherein said pharmacologic agent is selected from the group consisting of an endogenous compound, a drug, an herbal compound and a nutrient.

53. A method of claim 44 wherein said biological sample is a tumor sample.

54. A method of claim 44 wherein said biological sample is a sample of normal cells or tissues, or a derivative thereof.

55. A method of drug chemotherapy which comprises coadministering a drug and an agent that modulates the activity or expression of SXR.

56. A method of claim 53 which comprises coadministering a drug and an agent that downregulates the activity or expression of SXR.

57. A method of claim 53 which comprises coadministering a drug and an agent that upregulates the activity or expression of SXR.

58. A method of increasing the effectiveness of a drug which comprises coadministering said drug with an agent that modulates the actions of SXR.

59. A method of claim 53 wherein said agent is an SXR antagonist.

60. A method of claim 53 wherein said agent is an SXR agonist.

61. A method of claim 53 wherein said agent does not activate SXR.

62. A method of claim 53 wherein said drug is a taxane.